## REMARKS

Reconsideration of this application, as amended, is respectfully requested.

At the outset, Applicants gratefully acknowledge that the Examiner has kindly withdrawn all prior rejections of record.

After Applicants elected to prosecute method Claims 10-17 (Invention II) in the present application, the Examiner held the restriction requirement final in the Office action of January 7, 2003. Since the product claims (Invention I) had not been elected, the Examiner also indicated that the practice of rejoinder is not available to Applicants under the guidelines of M.P.E.P. § 821.04. Under the circumstances, therefore, Applicants are now canceling nonelected Claims 1-9 and 18 without prejudice to filing a divisional application in order to expedite matters and place the application in proper condition for an immediate allowance.

Turning to the current Office action, the Examiner has rejected Claims 10-12 and 14-16 under 35 U.S.C. § 103(a) as being unpatentable over Petersen *et al.* and Byars *et al.* in view of Liem *et al.* for reasons set forth on pages 4 and 5 of the Office action. Applicants respectfully traverse the rejection for the following reasons.

To establish a *prima facie* case of obviousness, the guidelines of M.P.E.P. § 706.02(j) and case law provide three basic criteria: (1) There must be some suggestion or motivation to modify the reference or to combine the reference teachings; (2) there must be a reasonable expectation of success; and (3) the combined references must teach or suggest all claim limitations. The guidelines of M.P.E.P. § 716.02(a) further indicate that a *prima facie* case of obviousness can be rebutted by evidence of results that are unexpected and significant, *i.e.*, the results are greater than those that would have been expected from the art to an unobvious extent and the results are of a significant, practical advantage.

In the case at hand, there is objective evidence that refutes any contention of *prima facie* obviousness. As proof of non-obviousness, the Examiner's attention is respectfully drawn to the teachings of the specification. The working examples demonstrate that the method of the present invention provides beneficial and unexpected results over those seen in the art.

By way of background, it is explained for the benefit of the Examiner that there has been an art-recognized problem in the administration of *Mycoplasma Hyopneumoniae* bacterin in that young animals had to be handled twice or too often in order to get sufficient immunity against



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disease. Attempts have been made to overcome that problem and reduce the number of times that the young animals need vaccination. Fort Dodge Animal Health ("FDAH") produces Suvaxyn ® RespiFend ® MH, that contains Carbopol ® (polyacrylic acid polymers) as an adjuvant, is recommended for semiannual revaccination but, undesirably, the vaccination schedule requires an initial two-dose vaccination, first shot for one-week old pigs, and a second booster shot two to three weeks after the primary vaccination. The two-dose vaccine has the obvious disadvantage of requiring a second handling of the young animals in order to provide full protection against disease (see discussion in the Background of the Invention on page 2, lines 5-12 of the specification). Another commercially available product Ingelvac® M. hyo manufactured by Boehringer Ingelheim, that contains an Impran® water-in-oil emulsion, is effective through one dose but only lasts 120 days. The pigs must be revaccinated every four months.

Example 3 on pages 12-19 of the specification shows that the new one-dose vaccination of the unique formulation of the present invention evidenced at least four months duration of immunity in pigs similar to the activity of Ingelvac® M. hyo. Then, surprisingly, Example 4 on pages 20-25 of the specification goes on to demonstrate that the novel vaccine of this invention and the claimed method of using it provide superior, long-term immunity to a full six months after the single dose administration.

The enhanced potency of the claimed formulation, currently marketed under the Tradename Suvaxyn® MH-One, is an improvement over the earlier two-shot formulation (Suvaxyn ® RespiFend ® MH) that did not contain the claim-recited mixture of metabolizable oil and a polyoxyethylene-polypropylene block copolymer. The present invention solves the art-recognized problem and unexpectedly gives a new and improved method in which the animals are immunized by a single vaccination that provides exceptional six-month immunity against mycoplasmal pneumonia disease without the booster shot. Quite advantageously, the new method for the prevention or amelioration of disease caused by *Mycoplasma hyopneumoniae* utilizes the claim-recited adjuvant formulation to significantly enhance the immunogenicity of the bacterin and elicit excellent protective immunity for 182 days (label claim) after a single dose of the vaccine. By alleviating handling stress, reducing vaccination time and decreasing labor time, the one-dose vaccination and long-acting immunity protection are very beneficial to the animal handlers and the animals themselves.



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Examining what the collective art fairly teaches to the ordinary practitioner, it is clear that the practitioner would not arrive at the claimed invention. The art fails to provide any suggestion or motivation of the desirability of combining the references and doing what the inventors have done. The practitioner would find real distinction between the claimed method and the cited references.

Before discussing what the primary reference of Petersen *et al.* teaches one of ordinary skill in the art, Applicants wish to inform the Examiner that the PCT application corresponds to U.S. Patent No. 5,565,205 that is displayed on the vial labels of the *Mycoplasma Hyopneumoniae* Bacterin injectable product marketed as Suvaxyn® RespiFend® MH by FDAH. In other words, Petersen *et al.* are directly connected with the injectable product on the market in which the method of vaccination mandates that a second dose follow two to three weeks after the first dose in order to achieve effective vaccination of the pigs.

Insofar as the literal teachings of Petersen *et al.* are concerned, the working examples of this reference show that the treatment groups received second injections two weeks after the first injections, and the standard two-shot vaccination method provided protection to 4 months of age (see Example 3 on pages 34-36 of the reference). While the reference implies that one dose of the bacterin can be injected into swine (page 12, lines 12-16), one of ordinary skill in the art would understand that the effects will not be long lasting and will not give meaningful protection. To achieve efficacy and long-term immunity up to four months, it is taught in the examples of Petersen *et al.* that the bacterin must be administered twice to the pig.

As the Examiner appreciates, Petersen *et al.* differ from the instant invention in not describing a mixture of metabolizable oil and a polyoxyethylene-polypropylene block copolymer. Contrary to the Examiner's opinion, however, Byars *et al.* do not teach or suggest that such a mixture should be combined with the *Mycoplasma hyopneumoniae* bacterin of Petersen *et al.* The opposite is true. Byars *et al.* actually teach away from the claimed invention.

In the "Introduction" on the first page of the reference, Byars *et al.* state that for some bacterial and viral diseases, the humoral responses provide adequate protection. For relatively weak antigens such as a number of viruses, parasites, fungi and tumors, cell-mediated immunity is the major protective mechanism of the host response. While the only antigen tested for the article was egg albumin, the "Discussion" on page 226 of the reference states that the authors' adjuvant formulation has been used with a pre-S protein of the hepatitis B virus, the formalin-



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inactivated feline leukemia virus and the simian type D retrovirus vaccines. There are no specific examples of any bacterin, let alone an implication that the *Mycoplasma hyopneumoniae* bacterin might be a weak antigen and require their adjuvant formulation. All in all, one of ordinary skill in the art would conclude based on the express teachings of Byars *et al.* that there would be no reason to combine the *Mycoplasma hyopneumoniae* bacterin with the adjuvant formulation of Byars *et al.* and no benefit would be expected from such a combination.

Furthermore, the authors describe their method of "Immunization" of the various preparations such that each guinea pig received egg albumin and MDP in the "primary immunization" and, at 4 weeks of age; a "boost" of antigen without MDP was given. There is absolutely no teaching or inference that the immunization process should omit the second booster shot. Plus, the studies only went to 49 days and did not show any long-term effects. The ordinary practitioner clearly would not expect good results and would not predict long-term immunity extending to six months in the absence of the art-recognized two-shot approach to vaccination. If anything, the authors effectively teach away from the claimed method in which there is single administration of the claimed vaccine to effectively vaccinate the pig.

Lastly, the adjuvant formulation taught by Byars *et al.* is not even a mere mixture of metabolizable oil and a polyoxyethylene-polypropylene block copolymer. For weak antigens, Byars *et al.* expressly teach an adjuvant formulation that includes a mixture of Pluronic L121 and squalene or squalane with muramyl dipeptides (MDP). The authors indicate on page 226 that while the formulation without added MDP does induce good secondary antibody titres in combination with the egg albumin, after a boost, the inclusion of [Thr$^1$]-MDP in the primary immunization gives superior results. Indeed, the authors never propose administering their adjuvant formulation without MDP in the primary immunization, and never recommend a single administration of vaccine to elicit protective immunity.

The secondary reference of Liem *et al.* does not provide the missing link to the two primary references to enable the ordinary practitioner to be able to arrive at the claimed invention. Liem *et al.* concern a killed whole cell culture of the *F. necrophorum* bacteria that is cultured for at least 10 hours to improve its antigenicity. The exemplification of the invention of Liem *et al.* shows that their vaccine is given by the conventional two-shot process, first at day 0 or day 1 and then again at day 21 (see paragraphs [0043] and [0052]). The studies stop at 50



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days. Although the reference implies numerous adjuvants could be used with the *F. necrophorum* bacteria (paragraph [0030]), the examples only show an oil-based adjuvant called SuprImm ® Oil. The bare disclosure of many different adjuvants that may be employed in a formulation containing *F. necrophorum* bacteria is very limited in its teachings. Without any doubt, the long generic list of possible choices does not describe or propose a specific mixture of metabolizable oil and a polyoxyethylene-polypropylene block copolymer, nor does it suggest that such a mixture should be combined with the *Mycoplasma hyopneumoniae* bacterin of Petersen *et al.*, let alone imply that the unique formulation with polyacrylic acid polymers would give long-term immunity after a single administration.

The combined art simply fails to render the claimed invention *prima facie* obvious. There is no description or suggestion in any of the cited references that single administration of the *Mycoplasma hyopneumoniae* bacterin when formulated according to the present invention could be successful at achieving effective immunity for six months. It is clear that there is no teaching in the combined art to suggest or motivate the ordinary practitioner to produce the claim-recited vaccine of the present application and practice the claimed method. The practitioner simply would not arrive at the claimed invention without inventive effort.

In view of the foregoing remarks, Applicants respectfully ask that the rejections of Claims 10-12 and 14-16 under 35 U.S.C. § 103(a) be withdrawn.

The Examiner has also rejected Claim 17 under 35 U.S.C. § 103(a) as being unpatentable over Petersen *et al.* as modified by Byars *et al.* and Liem *et al.* as applied to Claim 10 above and further in view of Burkhardt *et al.* and Potter *et al.* for reasons set forth on page 6 of the Office action. Applicants respectfully traverse the rejection for the following reasons.

First of all, as explained above, the combination of Petersen *et al.* as modified by Byars *et al.* and Liem *et al.* does not teach or suggest the mixture of metabolizable oil and a polyoxyethylene-polypropylene block copolymer in combination with polyacrylic acid polymers and the *Mycoplasma hyopneumoniae* bacterin. Secondly, the combined art does not describe or infer that the vaccine formulation made according to the present invention should be given as a single vaccination or would be effective in one dose. Thirdly, the ordinary practitioner would not expect or be able to predict the long-term, six-month immunity achieved from the novel vaccine of this invention based on the combined art of Petersen *et al.* as modified by Byars *et al.*



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and Liem *et al.* The tertiary references do not supply the missing teachings needed in order to arrive at the method of Claim 17.

Burkhardt *et al.* concern a cellfree extract preparation of *Haemophilus parasuis*. Patentees indicate that the *H. parasuis* may be combined with a broad variety of adjuvants (col. 3, lines 12-19) and may be formulated into multivalent vaccines that can contain *Mycoplasma hyopneumoniae* (col. 3, lines 38-47). However, they do not illustrate any multivalent vaccine formulations and only show monovalent vaccine formulations containing Diluvac® Forte adjuvant. Of major interest, the patentees expressly teach that the use of adjuvants is not necessary to provide immunogenic activity to their composition (col. 3, lines 17-19). They explicitly further instruct that the vaccine is most effective if administered in a series of at least two doses separated by two or three week intervals (col. 3, lines 22-24) plus exemplify vaccinating the pigs at 3 and 6 weeks (Example 5, col. 6, lines 29-32). Their studies only went to 9 weeks. It is clear that Burkhardt *et al.* do not provide any motivation to the ordinary practitioner to do what Applicants have done. The patent does not suggest the advantage of employing the mixture of metabolizable oil and a polyoxyethylene-polypropylene block copolymer in combination with polyacrylic acid polymers and, in no uncertain terms, effectively teaches away from the single administration of the multivalent vaccine. Applicants' excellent results are clearly unanticipated in light of the teachings of Burkhardt *et al.*

Reliance on Potter *et al.* is not justified in the Examiner's rejection of Claim 17. Potter *et al.* relate to subunit vaccines containing *H. somnus* outer membrane protein extracts enriched with iron-regulated proteins. Because this reference does not teach or suggest any of the limitations recited in Claim 17, Potter *et al.* should be removed as a cited reference.

In total sum, motivation to combine any of the reference teachings is lacking in the art. Nevertheless, even if the teachings were combined, the ordinary practitioner would still not arrive at the multivalent vaccine or its use as recited in Claim 17 and would not achieve what the inventors have done. There is no reason taught in the art to include the mixture of metabolizable oil and a polyoxyethylene-polypropylene block copolymer with polyacrylic acid polymers and the *Mycoplasma hyopneumoniae* bacterin; to eliminate the MDP taught as essential for immunity by Byars *et al.*; and not to administer the vaccine by the conventional two-step process. There is absolutely no reasonable expectation of success in a single administration of the vaccine prepared



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according to the teachings in the present application, and certainly no expectation at all of long-term immunity to six months. The *prima facie* case of obviousness has not been established in light of the unexpected and significant results exemplified by the vaccine of the present invention.

Consequently, Applicants respectfully ask that the rejection of Claim 17 under 35 U.S.C. § 103(a) be withdrawn.

It is noted that the Decision Granting Petition mailed December 13, 2004 had stated that the application was being referred to the Office of Initial Patent Examination for correction of the filing date to December 17, 2001 and issuance of a corrected filing receipt. Applicants have not yet received the corrected filing receipt. Moreover, while the Examiner recognizes in the instant Office action that the Petition was granted and the instant application is entitled to the filing date of December 17, 2001, the cover page for the Office communication of January 6, 2005 still shows the wrong filing date of 01/08/2002. Therefore, Applicants are herewith filing a Request for Corrected Filing Receipt to get the filing date corrected in the Official record in accord with the Decision on the Petition. A separate request for correction will be sent directly to the Assignment Division to reflect the correct filing and recordation date of December 17, 2001 in the Assignment data recorded on Reel/Frame Nos. 012484/0243.

Accordingly, it is believed that this application is now in condition for an allowance. Favorable treatment is respectfully urged.

Respectfully submitted,

WYETH

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